REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Amendments to Specification and Abstract

The specification and abstract have been amended to replace "sugar ester fatty acid" with "sucrose ester fatty acid", which is the appropriate term based on the original Japanese PCT application, upon which this application is based. Support for this amendment is also found in the Japanese priority application. A Substitute Specification and Abstract are attached. No new matter has been added to the application by this typographical correction.

Claim Amendments

Claim 1 has been amended to clarify that cefditoren pivoxil is present in the solid dispersion composition, and to incorporate the limitation from claim 2 regarding the range of sucrose ester fatty acid.

Claims 10 and 11 have been amended in a similar manner.

Claim 2 has been amended to include the phrase "on the basis of an amount equivalent to 100 mg efficacy of cefditoren pivoxil", in order to be consistent with claim 1.

The phrase "0.1 to 200 mg of the sucrose ester fatty acid and" has been deleted from claim 5, as this language is now recited in independent claim 1.

Claims 2 and 4 have been amended to delete the "preferably" language.

Claims 6, 8, 10 and 11 have been amended in order to provide proper antecedent basis for the claim limitations.

The claims have also been amended to replace "sugar ester fatty acid" with "sucrose ester fatty acid", which is the appropriate term based on the original Japanese PCT application, and the Japanese priority application for this application.

No new matter has been added to the application by the above-discussed amendments.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1-11 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is respectfully traversed for the following reasons.

The Examiner asserts that the amount of the various ingredients present in the composition is related to the efficacy of 100 mg of the drug cefditoren pivoxil. The Examiner takes the position that no indication is given in the specification as to how one determines the efficacy of 100 mg of cefditoren pivoxil so that one knows the basis on which the amount of other ingredients present is computed.

Applicants respectfully disagree with the Examiner's position for the following reasons.

"Efficacy" (potency) is a unit of an effective amount of antibiotics. Specifically, the "efficacy" is a unit commonly used for expressing an amount of an active moiety of an antibiotic. For example, when a certain antibiotic is provided as a salt, an amount of its salt-free form is expressed for an effective amount of the antibiotic.

Since cefditoren pivoxil is provided as an ester form, an amount of its ester-free form is expressed for an effective amount of cefditoren pivoxil.

For evidence, attached hereto are the relevant pages of the Japanese Pharmacopoeia Fifteenth Edition (English version), which indicates that the potency (efficacy) of cefditoren pivoxil is expressed as mass (potency) of cefditoren.

Further, also attached hereto is the notification by the Ministry of Health, Labour and Welfare in Japan, which indicates that the name and standards for the drugs concerned officially conform to those set forth in the Japanese Pharmacopoeia Fifteenth Edition.

MPEP 2163 (II)(A)(2) states that "[t]he analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art . . . Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v.*

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." (Emphasis added.)

As demonstrated by the discussion above, one skilled in the art would fully understand the meaning of the term "efficacy" as employed in Applicants' claims. Thus, in accordance with the standards set forth in the MPEP, "efficacy" is sufficiently defined in the specification. One of ordinary skill in the art could determine the efficacy of 100 mg of cefditoren pivoxil so that the other ingredients can be compared based on the cefditoren pivoxil.

Therefore, the subject matter set forth in Applicants' claims is sufficiently described in the specification, and the above rejection should be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-11 as being indefinite under 35 U.S.C. § 112, second paragraph is respectfully traversed for the reasons stated below.

The Examiner states that "if the cefditoren pivoxil need be present in the composition and the amount of the other ingredients cannot be determined, rendering the metes and bounds of the claims indefinite". As discussed above, Applicants have amended claim 1 to clarify that cefditoren pivoxil is present in the solid dispersion composition.

Additionally, according to MPEP 2173.02, the definiteness of claim language must be analyzed, not in a vacuum, but in light of the specification, the teachings of the prior art and the interpretation which would be given to the claim by one of ordinary skill in the art. As Applicants have shown (and discussed above), "efficacy" is understood by those skilled in the art as a unit used for expressing an amount of an active moiety of an antibiotic. Thus, even if the amounts of the other ingredients are defined by absolute mass, one of ordinary skill in the art could determine the amounts of the other ingredients.

Accordingly, the above-rejection should be withdrawn.

The rejection of claims 1, 2, 4, 10 and 11 as being indefinite under 35 U.S.C. § 112, second paragraph has been rendered moot by the above-discussed amendments.

Patentability Arguments

The patentability of the present invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Double Patenting Rejection

The provisional rejection of claims 1-5, 7 and 9 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4-9 and 12 of co-pending U.S. Application No. 10/530,046 has been overcome by the filing of a Terminal Disclaimer, together with the required fee. Applicants submit the Terminal Disclaimer for the sole purpose of expediting prosecution, and do not acquiesce to the Examiner's rejection.

Rejections Under 35 U.S.C. § 103(a)

JP 60132918 (JP '918) in view of the Merck Index

The rejection of claims 1, 2 and 8 under 35 U.S.C. § 103(a) as being unpatentable over the English abstract of JP 60132918 (JP '918) in view of the Merck Index for cefditoren is respectfully traversed.

Position of the Examiner

The Examiner takes the position that JP '918 discloses compositions comprising a cephalosporin antibiotic and a sucrose fatty acid ester which had improved oral absorbability, and which can be administered in solid dosage forms. The Examiner asserts that the amount of the sucrose ester fatty acid is present between 0.01 and 50% by weight when compared to the cephalosporin antibiotic. The Examiner admits that JP '918 fail to disclose the amount of these ingredients by absolute weight and does not exemplify cefditoren pivoxil as a cephalosporin antibiotic.

The Examiner asserts that cefditoren is a third generation cephalosporin and the active metabolite of the pivaloyloxymethyl ester prodrug known as cefditoren pivoxil (Merck). The Examiner asserts that cefditoren pivoxil is a functional equivalent to the cephalosporin disclosed

in JP '918. The Examiner states that if one formulated a composition with 100 mg of cefditoren pivoxil, based on the weight ratios disclosed in JP '918, the composition could contain between 0.01 and 50 mg of sucrose fatty acid ester.

The Examiner also admits that how long the cefditoren pivoxil is maintained in amorphous state when suspended in water (Applicants' claim 8) is not disclosed in the prior art.

Applicants' Arguments

Applicants respectfully disagree with the Examiner's position for the following reasons.

As discussed above, JP '918 discloses that a combination of cephalosporin antibiotic and a sucrose fatty acid ester improves oral absorbability. However, the reference does not refer to the problem to be solved by the present invention, i.e. that cefditoren pivoxil is easily converted from an amorphous form to a crystalline form in solution. Thus, the reference clearly fails to disclose that the amorphousness of cefditoren pivoxil, which is not even disclosed by JP '918, can be prevented by adding sucrose ester fatty acid to a solid dispersion composition of cefditoren pivoxil.

Furthermore, at the time of the priority date of the present application, one of ordinary skill in the art would refrain from adding a surfactant, such as a sucrose ester fatty acid, into a medicament. At the time of the priority date of the present application, the understanding of those skilled in the art was that the addition of a surfactant into a medicament would accelerate the crystallization of an active ingredient when the medicament is dissolved in an aqueous solution. Further, when a medicament containing a surfactant is dissolved in an aqueous solution, a supersaturated solution of the active ingredient forms on the surface of the medicament. When such a supersaturated solution moves away from the medicament, a supersaturated unsolved portion would generate as a crystal.

In support of the above discussion. Applicants direct the Examiner's attention to Reference Example 2 of the specification, which demonstrates that when a surfactant other than a sugar ester fatty acid is used, (in this case, Tween 80), the crystallization of amorphous cefditoren pivoxil is accelerated. (Please see Table 3 on page 11 of Applicants' original specification for the results based on Reference Example 2, in comparison with examples which employed

sucrose ester fatty acid.)

Accordingly, at the time of the present invention, one skilled in the art would not have combined the teachings of the references in the manner suggested by the Examiner.

For these reasons, the subject matter of the above-rejected claims is clearly patentable over the cited combination of references.

Kikkoji et al. (EP 0629404) in view of JP 60132918 (JP '918)

The rejection of claims 1, 3-7 and 9-11 under 35 U.S.C. § 103(a) as being unpatentable over Kikkoji et al. (EP 0629404) in view of the English abstract of JP 60132918 (JP '918) is respectfully traversed.

Position of the Examiner

The Examiner takes the position that Kikkoji et al. disclose pharmaceutical compositions for oral administration of cefditoren pivoxil and hydroxypropylcellulose. The Examiner admits that Kikkoji et al. fail to teach the inclusion of a sugar fatty acid ester, as well as a liquid composition in which the solid composition is dissolved or suspended in a liquid.

The Examiner relies upon JP '918 for the reasons previously stated. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to combine the teachings of Kikkoji et al. and JP '918.

Applicants' Arguments

Applicants respectfully disagree with the Examiner's position for the following reasons.

EP '404 discloses the use of hydroxypropylcellulose in cefditoren pivoxil compositions. However, EP '404 does not refer to the problem to be solved by the present invention, i.e. that cefditoren pivoxil is easily converted from an amorphous form to a crystalline form in a solution, nor does it disclose that the amorphousness of cefditoren pivoxil can be prevented by adding sugar ester fatty acid to a solid dispersion composition of cefditoren pivoxil.

Additionally, for the reasons discussed above, at the time of the priority date of the present application, one of ordinary skill in the art would have refrained from adding a surfactant,

such as a sugar ester fatty acid, into a medicament. Thus, at the time of the present invention, one skilled in the art would not have combined the teachings of the references in the manner suggested by the Examiner.

For these reasons, the subject matter of the above-rejected claims is clearly patentable over the cited combination of references.

Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

Shigeru CHIKASE et al.

By:_____

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July 14, 2008

Attachments: Substitute Specification (marked up version)
Substitute Specification (clean version)

Japanese Parmacopoeia Fifteenth Edition

Operating conditions—

Proceed as directed in the Assay under Cefdinir.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of cefdinir are not less than 2000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of cefdinir is not more than 1.0%.

Particle size ⟨*6.03*⟩ It meets the requirement of fine granules of the Powders.

Assay Powder, if necessary, and weigh accurately an amount of Cefdinir Fine Granules, equivalent to about 0.1 g (potency) of Cefdinir according to the labeled amount, add 70 mL of 0.1 mol/L phosphate buffer solution, pH 7.0, shake for 30 minutes, and add 0.1 mol/L phosphate buffer solution, pH 7.0 to make exactly 100 mL. Centrifuge at 3000 revolutions per minute for 10 minutes, pipet 4 mL of the supernatant liquid, add 0.1 mol/L phosphate buffer solution, pH 7.0 to make 20 mL, and use this solution as the sample solution. Separately, weigh accurately an amount of Cefdinir Reference Standard, equivalent to about 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution, pH 7.0 to make exactly 100 mL, and use this solution as the standard solution. Proceed as directed in the Assay under Cefdinir.

$$\text{Amount [mg (potency)] of cefdinir } (C_{14}H_{13}N_5O_5S_2) = W_S \times (A_T/A_S) \times 5$$

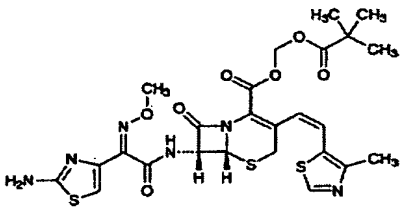
W_S: Amount [mg (potency)] of Cefdinir Reference Standard

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cefditoren Pivoxil

セフジトレン ピボキシル



$C_{25}H_{28}N_6O_7S_3$: 620.72

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetylamino]-3-[(1*Z*)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [*117467-28-4*]

Cefditoren Pivoxil contains not less than 770 μg (potency) and not more than 820 μg (potency) per mg, calculated on the anhydrous basis. The potency of Cefditoren Pivoxil is expressed as mass (potency) of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58).

Description Cefditoren Pivoxil occurs as a light yellowish white to light yellow crystalline powder.

It is sparingly soluble in methanol, slightly soluble in acetonitrile and in ethanol (95), very slightly sobuble in diethyleter and practically insoluble in water.

It dissolves in dilute hydrochloric acid.

Identification (1) Dissolve 5 mg of Cefditoren Pivoxil in 3 mL of hydroxylammonium chloride-ethanol TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron (III) sulfate TS and shake: a red-brown color develops.

(2) Dissolve 1 mg of Cefditoren Pivoxil in 1 mL of dilute hydrochloric acid and 4 mL of water, add 3 drops of sodium nitrite TS under ice-cooling, shake, and allow to stand for 2 minutes. Then add 1 mL of ammonium amidosulfate TS, shake well, and allow to stand for 1 minute, and add 1 mL of *N,N*-diethyl-*N'*-1-naphthylethylenediamine oxalate TS: a purple color develops.

(3) Determine the absorption spectrum of a solution of Cefditoren Pivoxil in methanol (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry ⟨*2.24*⟩, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Cefditoren Pivoxil Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the spectrum of a solution of Cefditoren Pivoxil in deuterated chloroform for nuclear magnetic resonance spectroscopy (1 in 50), using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound, as directed under Nuclear Magnetic Resonance Spectroscopy ⟨*2.21*⟩ (^{1}H): it exhibits single signals A, B and C, at around δ 1.1 ppm, at around δ 2.4 ppm and at around δ 4.0 ppm, double signals D and E, at around δ 6.4 ppm and at around δ 6.7 ppm, and a single signal F at around δ 8.6 ppm. The ratio of integrated intensity of each signal A:B:C:D:E:F, is about 9:3:3:1:1:1.

Absorbance ⟨*2.24*⟩ $E^{1\%}_{1cm}$ (231 nm): 340 – 360 (50 mg, methanol, 2500 mL).

Optical rotation ⟨*2.49*⟩ $[\alpha]_D^{20}$: −45 – −52° (50 mg, methanol, 10 mL, 100 mm).

Purity (1) Heavy metals ⟨*1.07*⟩—Proceed with 2.0 g of Cefditoren Pivoxil according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Being specified separately.

(3) Residual solvents—Being specified separately.

Water ⟨*2.48*⟩ Not more than 1.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition Being specified separately.

Assay Conduct this procedure without exposure to daylight, using light-resistant vessels. Weigh accurately an amount of Cefditoren Pivoxil and Cefditoren Pivoxil Reference Standard, equivalent to about 40 mg (potency), dissolve in 40 mL of acetonitrile, add exactly 10 mL each of the internal standard solution, and add acetonitrile to make 100 mL, and use these solutions as the sample solution and standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography ⟨*2.01*⟩ according to the following conditions,

and calculate the ratios, Q_T and Q_S, of the peak area of cefditoren pivoxil to that of the internal standard.

Amount [μg (potency)] of cefditoren ($C_{19}H_{18}N_6O_5S_3$) = $W_S \times (Q_T/Q_S) \times 1000$

W_S: Amount [mg (potency)] of Cefditoren Pivoxil Reference Standard

Internal standard solution—A solution of propyl *p*-hydroxybenzoate in acetonitrile (1 in 200).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 1.58 g of ammonium formate in 900 mL of water, adjust to pH 6.0 with diluted formic acid (1 in 250), and add water to make 1000 mL. To 450 mL of this solution add 275 mL of acetonitrile and 275 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefditoren pivoxil is about 15 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and cefditoren pivoxil are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of cefditoren pivoxil to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cefditoren Pivoxil Fine Granules

セフジトレン ピボキシル細粒

Cefditoren Pivoxil Fine Granules contain not less than 90.0% and not more than 110.0% of the labeled amount of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58).

Method of preparation Prepare in the form of very fine granules as directed under Powders, with Cefditoren Pivoxil.

Identification To an amount of powdered Cefditoren Pivoxil Fine Granules, equivalent to 0.1 g (potency) of Cefditoren Pivoxil according to the labeled amount, add 10 mL of acetonitrile, shake vigorously, and filter. To 1 mL of the filtrate add acetonitrile to make 50 mL. To 1 mL of this solution add acetonitrile to make 20 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 230 nm and 234 nm.

Purity Related substances—Being specified separately.

Loss on drying <*2.41*> Not more than 4.5% (0.5 g, reduced pressure not exceeding 0.67 kPa, 60°C, 3 hours).

Uniformity of dosage units <*6.02*> The granules in single-unit container meet the requirement of the Mass variation test.

Dissolution Being specified separately.

Particle size <*6.03*> It meets the requirement of fine granules of the Powders.

Assay Conduct this procedure without exposure to daylight, using light-resistant vessels. Weigh accurately an amount of powdered Cefditoren Pivoxil Fine Granules, equivalent to about 40 mg (potency) of Cefditoren Pivoxil according to the labeled amount, add 70 mL of diluted acetonitrile (3 in 4), and shake vigorously. To this solution add exactly 10 mL of the internal standard solution, then add acetonitrile to make 100 mL, filter, and use the filtrate as the sample solution. Separately, weigh accurately about 20 mg (potency) of Cefditoren Pivoxil Reference Standard, dissolve in 20 mL of acetonitrile, add exactly 5 mL of the internal standard solution, then add acetonitrile to make 50 mL, and use this solution as the standard solution. Proceed as directed in the Assay under Cefditoren Pivoxil.

Amount [mg (potency)] of cefditoren ($C_{19}H_{18}N_6O_5S_3$) = $W_S \times (Q_T/Q_S) \times 2$

W_S: Amount [mg (potency)] of Cefditoren Pivoxil Reference Standard

Internal standard solution—A solution of propyl parahydroxybenzoate in acetonitrile (1 in 200)

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cefditoren Pivoxil Tablets

セフジトレン ピボキシル錠

Cefditoren Pivoxil Tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58),

Method of preparation Prepare as directed under Tablets, with Cefditoren Pivoxil.

Identification To an amount of powdered Cefditoren Pivoxil Tablets, equivalent to 35 mg (potency) of Cefditoren Pivoxil according to the labeled amount, add 100 mL of methanol, shake, and filter. To 5 mL of the filtrate add methanol to make 100 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 229 nm and 233 nm.

Purity Related substances—Being specified separately.

Loss on drying <*2.41*> Not more than 4.0% (0.5 g, reduced pressure not exceeding 0.67 kPa, 60°C, 3 hours).

Uniformity of dosage units <*6.02*> Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Cefditoren Pivoxil Tablets add 12.5 mL of the 1st fluid for disintegration test, shake vigorously, add

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The Ministry of Health, Labour and Welfare Ministerial Notification No. 285

Pursuant to Paragraph 1, Article 41 of the Pharmaceutical Affairs Law (Law No. 145, 1960), the Japanese Pharmacopoeia (hereinafter referred to as "new Pharmacopoeia"), which has been established as follows*, shall be applied on April 1, 2006, and the Ministry of Health, Labour and Welfare Ministerial Notification No. 111 (Matter of Establishing the Japanese Pharmacopoeia; hereinafter referred to as "previous Pharmacopoeia"), issued in 2001, shall be abolished on March 31, 2006. However, in the case of drugs which are listed in the new Pharmacopoeia (limited to those listed in the previous Pharmacopoeia) and drugs which have been approved as of April 1, 2006 as prescribed under Paragraph 1, Article 14 of the same law [including drugs the Minister of Health, Labour and Welfare specifies (the Ministry of Health and Welfare Ministerial Notification No. 104, 1994) as those exempted from marketing approval pursuant to Paragraph 1, Article 14 of the Pharmaceutical Affairs Law (hereinafter referred to as "drugs exempted from approval")], the Name and Standards established in the previous Pharmacopoeia (limited to part of the Name and Standards for the drugs concerned) may be accepted to conform to the Name and Standards established in the new Pharmacopoeia before and on September 30, 2007. In the case of drugs which are listed in the new Pharmacopoeia (excluding those listed in the previous Pharmacopoeia) and drugs which have been approved as of April 1, 2006 as prescribed under Paragraph 1, Article 14 of the same law (including those exempted from approval), they may be accepted as those being not listed in the new Pharmacopoeia before and on September 30, 2007.

Jiro Kawasaki
The Minister of Health, Labour and Welfare

March 31, 2006

Referring the next title to this book: "The Japanese Pharmacopoeia".

(The text referred to by the term "as follows" are omitted here. All of them are made available for public exhibition at the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, at each Regional Bureau of Health and Welfare, and at each Prefectural Office in Japan).

*The term "as follows" here indicates the contents of the Japanese Pharmacopoeia Fifteenth Edition from General Notices to Ultraviolet-visible Reference Spectra (pp. 1 - 1654).